

Renal Manifestations in Juvenile Idiopathic Arthritis (JIA) And The Use Of Monoclonal Antibodies For Its Treatment: A Systematic Review

Umaima Fatima, Aaiyat Sheikh, Chaitanya S. Puvvada, Faiza H. Soomro, Hafsa A. Osman Merna Haridi, Natalie A. Gonzalez, Sana M. Dayo, Ann Kashmer Yu
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Abstract

Juvenile idiopathic arthritis (JIA) is a group of chronic childhood arthropathies in which various joints are affected. Along with the joints being involved, long-standing arthritis can lead to other systemic involvements. Eyes, kidneys, and skin are some examples. It is no surprise that we come across many patients suffering from renal complications due to long-standing JIA. This systematic review aimed to focus on the renal involvement seen in JIA and the use of monoclonal antibodies in its treatment. A systematic review was performed using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and researching studies on databases like PubMed, PubMed Central, and Google Scholar on June 26, 2022. Assessment tools like Cochrane, SANRA, and JBI Tool were used for quality assessment and the selection of articles. Followed by the quality assessment, seven studies were included in the final selection. These were two randomized control trials, four case reports, and one literature review. In conclusion, many cases involving renal complications along with JIA were seen, and Tocilizumab has proved to be efficacious in improving renal complications in JIA. This review encourages further study and research into the topic to understand the effects on JIA and the use of monoclonal antibodies as therapy.

Introduction

Similar to adults, children can have arthritis. Juvenile idiopathic arthritis (JIA) is the most typical kind of long-lasting or chronic arthritis that affects children. Joint inflammation (arthritis) can cause joint pain, swelling, warmth, stiffness, and loss of mobility. JIA is a general term for a number of distinct chronic illnesses involving joint inflammation. JIA may only last a brief period, such as a few months or years, but it is occasionally a chronic illness that requires care well into adulthood.

JIA. The patient is a seven-year-old boy from Iran. He showed a history of JIA since age one and now suffers from generalized edema and hypertension. He was in his usual state of health until he was one year old when he developed joint pain in his ankle and knee, for which he did not seek medical attention. The family history was unremarkable[10]. The renal clinic examinations revealed an oedematous child with no apparent respiratory distress syndrome. His blood pressure was 130/90 mmHg (higher than the 95th percentile). Severe arthritis and bone deformities affected the large and small joints in his hands and feet. The rest of the examination was unremarkable. Skeletal radiography revealed findings that were consistent with JIA [10].

An angiotensin-converting enzyme (ACE) inhibitor and a calcium channel blocker were used to control the patient's blood pressure. A 24-hour urine collection method revealed significant proteinuria. A renal biopsy was done, and under polarised microscopy, Congo red staining was shown to be positive with apple green birefringence. There was also some tubular atrophy and interstitial fibrosis, which confirmed renal amyloidosis [10].

In another case report by Małgorzata Kwiatkowska et al., 2015 a 16-year-old boy has had JIA since he was two years old. The disease manifested quickly, with fevers reaching 40°C, transient rashes, enlarged liver, spleen, and lymph nodes, and inflammation of the knee and ankle joints beginning in the sixth week of the disease. The symptoms significantly reduced the child's independent mobility [11].

reviewing such case reports, we know the effects of long-standing JIA on kidneys.

The term "idiopathic" refers to a condition whose cause is unknown. JIA starts when the immune system overreacts and generates inflammation, albeit the precise causes are unknown [1]. According to a comparison of epidemiological research on JIA, the yearly incidence ranges from 2.6 to 23 cases per 100,000 children per year, with an estimated prevalence of 15.7-140 instances per 100,000 children [2].

Renal involvement is a rare occurrence in juvenile rheumatoid arthritis (JRA). We went through various studies and case reports that state the involvement of the kidney in JIA. We also went through the treatment procedure followed and results which usually involved monoclonal antibodies.

In the biologic era, nonsteroidal anti-inflammatory medications, glucocorticoids, and/or conventional disease-modifying antirheumatic medications were used to treat sJIA. Unfortunately, almost half of patients still have active disease, and many more suffer from the cumulative side effects of long-term glucocorticoid therapy. Biologics that target interleukin 1 (IL-1) (such as anakinra, canakinumab, and rilonacept) and interleukin 6 (IL-6) (such as Tocilizumab) have greatly improved sJIA patient results lately.

While the origin of the immune system's overreaction in JIA is unknown, scientists have identified some of the molecules that contribute to inflammation in some forms of the disease. We now know that three molecules—TNF-alpha, IL-6, and IL-1—create inflammation in many children with JIA joints. This has led to new therapies that specifically target these molecules. A few such target molecules are monoclonal antibodies [4].

A monoclonal antibody is created by cloning a single white blood cell. All subsequent antibodies generated in this manner may be traced back to a single parent cell. Monoclonal antibodies have monovalent affinity, which means they exclusively bind to the same epitope. These have been increasingly used in the treatment of many child-related auto-inflammatory diseases. Omalizumab, adalimumab, ustekinumab, infliximab, golimumab, canakinumab, and Tocilizumab, are a few monoclonal antibodies to name that are used in the treatment of JIA [4].

Despite the current literature, more studies are needed to understand the long-term systemic effects of JIA and the efficacy of monoclonal antibodies in its treatment.

Use of Monoclonal antibodies in juvenile idiopathic arthritis

In arthritis, the safety and effectiveness of mAbs targeting the IL-6 receptor have been proven.

In another RCT by Ruperto et al., canakinumab was used to detect its efficacy in JIA.

In the RCT by Ruperto, in around 33 percent of the patients, a single injection of canakinumab resulted in inactive illness in as little as 15 days and reached JIA ACR 30 response. The dose administered was 4 mg per kilogram of body weight per month. It is an anti-IL-1 β monoclonal antibody. Thus the monoclonal antibody canakinumab may improve symptoms of JIA. A drastic reduction in fever was observed [12].

Serious adverse events such as macrophage activation syndrome and varicella were also reported [12].

A study on the use of adalimumab in JIA was evaluated in a literature review by Katherine Anne B. Marzan. It was a multicenter, randomised, stratified, double-blind, placebo-controlled trial of children and adolescents aged 4–17 years with an active moderate polyarticular course. All patients were stratified based on methotrexate use and received subcutaneous injections of 24 mg/m² (up to 40 mg) of adalimumab every other week throughout the 16-week open-label lead-in period. In the next 32-week double-blind treatment phase, responders (defined as patients with an ACR Pedi 30) were randomised within their stratum to either adalimumab or placebo. Patients who completed the double-blind treatment period were eligible for a 2-year open-label adalimumab treatment extension period [15].

16 weeks of the open-label lead-in were completed by 160 of the 171 JIA patients who were enrolled. ACR Pedi 30 was attained by 74.4% of patients receiving adalimumab monotherapy and 94.1% of patients receiving adalimumab and methotrexate together. 59% and 82% of patients received an ACR Pedi 70, respectively. More importantly, nearly equal numbers of patients in both strata achieved an ACR Pedi 90 (28.2% methotrexate versus 25.6% non-methotrexate), indicating near-clinical remission. Clinical response was rapid, with 67% and 77% of patients in both groups achieving an ACR Pedi 30 within 2-4 weeks of treatment, respectively [15].

In the 12-week, double-blind RCT by De Benedetti et al., 112 children, aged 2 to 17, with active systemic JIA

Hence a systematic review was conducted to understand the impact of chronic JIA on organs such as the kidney.

This systematic review reveals the renal manifestations of JIA and its treatment with different monoclonal antibodies.

Method

For this systematic review, we used three databases: PubMed, Google Scholar, and PubMed Central. In addition, the following keywords were used juvenile idiopathic arthritis, renal manifestations, renal complications, and monoclonal antibodies.

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 standards, which were developed to make systematic review reporting more thorough and transparent, were followed throughout the study.

Articles from the previous ten years were included from 2012-2022. Free full-text articles were included. In addition, published Randomized control trials (RCT), case reports, literature reviews, and systematic reviews were considered. For Google scholar, the initial 250 articles were reviewed due to many articles in abundance. No restrictions were made regarding the sex, race, and ethnicity of the patients involved.

Articles not in English, paid articles, articles older than ten years, and grey literature were excluded. The last date to extract articles from the databases was June 26, 2022. The PIO strategy was used in the formation of the research question, which was renal manifestations (outcome) seen in patients with juvenile idiopathic arthritis (Population) and the use of monoclonal antibodies in its treatment (intervention). All references were grouped together using ENDNOTE and alphabetized using Microsoft excel 2021 for duplicate removal.

The systematic review is based on various studies like randomized control trials (RCT), literature reviews, and case reports. The RCTs were assessed based on the Cochrane bias tool [5]. The case reports were evaluated based on the JB tool for case reports [6]. The literature review was assessed using the SANRA assessment tool [7].

A systematic review was then conducted following the Prisma guidelines checklist 2020 [8]

(6 months and poor responses to glucocorticoids and NSAIDs) were randomised to receive intravenously injected placebo or tocilizumab, an anti-interleukin-6 receptor antibody [13].

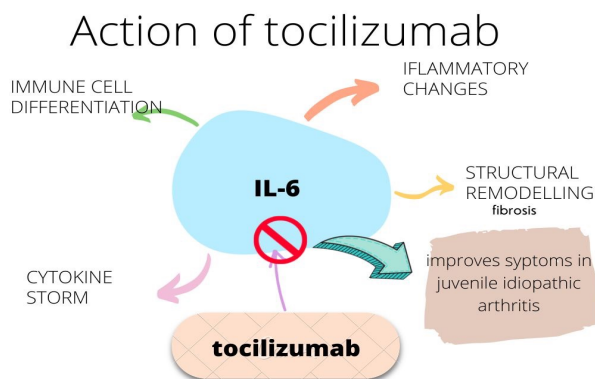
The primary outcome of JIA is based on the number of joints with active arthritis, the number of joints with a limited range of the physician's global assessment of disease activity (with scores ranging from 0 to 100 and higher scores indicating more active disease), the parent's or patient's global assessment of overall well-being (with scores ranging from 0 to 100 and higher scores indicating more active disease), physical function (as assessed with the use of the Disability Index of the Childhood Health Assessment Questionnaire [CHAQ-DI], with scores ranging from 0 to 3 and higher scores indicating more disability) and erythrocyte sedimentation rate [13].

Physicians global assessment of overall disease activity (10 cm visual analog scale)
 Parent/patient assessment of overall well-being (10 cm visual analog scale)
 Functional ability (Childhood Health Assessment Questionnaire)
 Number of joints with active arthritis
 Number of joints with limited range of motion
 Erythrocyte sedimentation rate

The primary outcome was the proportion of patients who had a JIA ACR 30 response, defined as an improvement of 30% or more in three or more of the six variables of the ACR core set for JIA, with no more than one variable worsening by more than 30%, and an absence of fever.

Thus Tocilizumab proved effective in treating severe, long-lasting systemic JIA. Infection, neutropenia, and elevated aminotransferase levels were only a few of the frequent adverse effects. [13]

The action of Tocilizumab is shown in figure 2.



The PubMed Mesh strategy used is shown in table 1 below:

Topic	Keywords
Juvenile idiopathic arthritis AND renal manifestations AND monoclonal antibodies	Arthritis OR rheumatism OR inflammatory disease OR degenerative joint disease OR juvenile idiopathic arthritis ("Arthritis/complications"[Mesh] OR "Arthritis/diagnosis"[Mesh] OR "Arthritis/drug therapy"[Mesh] OR "Arthritis/etiology"[Mesh] OR "Arthritis/genetics"[Mesh] OR "Arthritis/pathology"[Mesh] OR "Arthritis/physiopathology"[Mesh] OR "Arthritis/therapy"[Mesh]) AND monoclonal antibodies OR biologics OR ("Antibodies, Monoclonal/administration and dosage"[Mesh] OR "Antibodies, Monoclonal/adverse effects"[Mesh] OR "Antibodies, Monoclonal/drug effects"[Mesh] OR "Antibodies, Monoclonal/genetics"[Mesh] OR "Antibodies, Monoclonal/immunology"[Mesh] OR "Antibodies, Monoclonal/pharmacokinetics"[Mesh] OR "Antibodies, Monoclonal/pharmacology"[Mesh] OR "Antibodies, Monoclonal/therapeutic use"[Mesh]) AND Kidney OR high BUN OR renal failure OR chronic kidney disease OR ("Kidney/blood supply"[Mesh] OR "Kidney/complications"[Mesh] OR "Kidney/drug effects"[Mesh] OR "Kidney/injuries"[Mesh] OR "Kidney/pathology"[Mesh] OR "Kidney/physiopathology"[Mesh] OR "Kidney/statistics and numerical data"[Mesh] OR "Kidney/therapy"[Mesh] OR "Kidney/transplantation"[Mesh])

Results

Figure 1 shows the Prisma diagram for this systematic review.

A total of 486 articles were collected from databases like PubMed, Google Scholar, and PubMed Central. The duplicates were then eliminated. Three hundred forty-seven articles were then taken out based on their title. Articles not in English and paid articles were then removed. Forty articles were then used for the quality check. Each assessment tool had its criteria and different scoring. Hence a score of more > than 70% was taken into consideration. Subsequently, seven articles were used including RCTs, Case reports, and literature reviews.

In another case report by Huang et al., given the favorable impact of JAK inhibitors in RA, oral tofacitinib has started the dose being 2.5mg twice daily along with methylprednisolone 4mg. In addition, tofacitinib was titrated to a dosage of 5 mg twice daily after two weeks based on existing pharmacokinetic data in this patient, who was 13 years old at the time of therapy.

Interestingly, her arthritis gradually improved over the following two months after nearly two years of severe joint inflammation. The acute-phase reactants were significantly reduced, and serum ferritin levels were within normal ranges (100.3 ng/mL) [14].

A 16-year-old male youngster with long-term JIA who also had nephrotic syndrome was the subject of a case report by Magorzata Kwiatkowska. In all glomeruli, like in the case of hyalinization, a kidney biopsy revealed amyloidosis and evident segmental lesions. However, the child's health rapidly improved after receiving the prescribed amount of tocilizumab (240 mg), and subsequent blood tests two weeks later verified that inflammatory indicators had returned to normal [11].

The boy's condition is satisfactory after 42 months of tocilizumab therapy. There is no discomfort or joint edema, no nephrotic syndrome symptoms, the liver is average size, laboratory test results are normal, and daily proteinuria is less than 0.25 g/24 h. (no proteinuria in random tests) [11].

Using Tocilizumab:

The effectiveness of tocilizumab treatment for systemic JIA that is not responding to standard therapy is being supported by an increasing number of publications. There are, however, very few reports on Tocilizumab's positive benefits on JIA amyloidosis, notably in treating nephrotic syndrome [11].

A dose of 8 mg/kg was the starting dose after using several other drugs like glucocorticoids, etanercept, and cyclophosphamide, which showed minimal improvement. However, the child's condition slowly but gradually improved, especially concerning the joints – pain and edema decreased, and the range of motion increased [11].

After the 10th tocilizumab treatment, inflammatory indicators returned to normal. Beginning with the first dose of Tocilizumab, proteinuria gradually decreased (18 to 8 g/24hr) until it was below 1.0 g/24 hours by the 15th treatment [11].

The full articles remaining were assessed for quality assessment and risk of bias using tools depending on the study type: RCTs, Cochrane Collaboration Risk of Bias Tool (CCRBt);

Assessment of RCTs using CCRBT is shown below in table 1

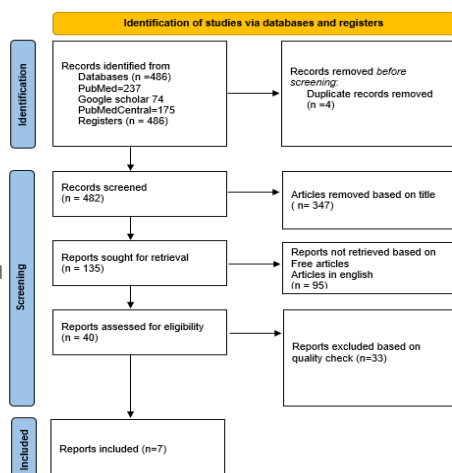
Study	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions	Risk of bias due to missing outcome	Risk of bias in the measurement of the outcome	Risk of bias in the selection of the reported result
De Benedetti et al [13].	LOW	LOW	LOW	LOW	UNCLEAR
Ruperto et al [12].	LOW	LOW	LOW	LOW	LOW

Both the RCTs assessed in the review used the CCRBT and had a "LOW RISK" bias.

The case reports were assessed using the JB tool, and a score of >70% was considered.

This review takes into consideration cases with renal involvement, its treatment, its treatment using monoclonal antibodies, comparisons between different monoclonal antibodies, and their side effects. All the outcomes are related to juvenile idiopathic arthritis.

A flow diagram showing the screening process and study selection is presented in Figure 1.



Thus Tocilizumab is proven to be efficacious in reducing inflammatory markers seen in JIA. It also effectively reduces proteinuria and improves nephrotic syndrome associated with JIA. Hence the use of Tocilizumab as a therapy for JIA to improve renal involvement can be considered [11].

Also, Tocilizumab does not appear to be related to an increased risk of a macrophage-activating syndrome like other monoclonal antibodies. [11]

Limitations

Due to the limited number of studies that report renal involvement in JIA, further research and studies should be carried out for better understanding. Furthermore, given that the use of monoclonal antibodies is an emerging application as therapy, much more studying should be done on its use in the treatment of JIA. Furthermore, more clinical trials are required to assess the impact of monoclonal antibodies on the systemic consequences of JIA. In addition, grey literature was omitted, and several articles written in their languages needed to be considered. Finally, articles published only between 2012-2022 were considered, which also stands as a limitation.

Conclusion

Renal complications are also seen in long-standing juvenile idiopathic arthritis. Complications such as nephrotic syndrome and amyloidosis have been reported. Monoclonal antibodies are the emerging field of drugs used to treat various auto-inflammatory diseases. Reports have shown the safety and effectiveness of monoclonal antibodies in treating juvenile idiopathic arthritis. Monoclonal antibodies targeting specific inflammatory pathways have shown potential in the treatment of these manifestations, with improvements in renal function and disease activity observed. Canakinumab tofacitinib and Tocilizumab have been highly effective. Tocilizumab has also improved systemic effects, such as the mentioned renal complications. Further research, including well-designed randomized controlled trials, is needed to establish the long-term safety, optimal dosing, and efficacy of different monoclonal antibodies in managing renal manifestations in JIA.

Study characteristics

Characteristics of the articles selected are shown in tables 2 and 3.

Author, year of publication.	Organ involved	Country	Number of patients	Age and sex	Type of Study	Conclusion
Chantarogh et al, 2017[9]	Kidney	-	1	19 years; female	Case report	Renal amyloidosis, along with JIA
Maleknejad M et al, 2015[10]	Kidney	Iran	1	7 years; male	Case report	Renal amyloidosis along with the nephrotic syndrome
Małgorzata Kwiatkowska, et al, 2015 [11]	kidney	-	1	16 years; male	Case report	a nephrotic syndrome due to secondary type A amyloidosis

Author	Study type	drug	Intervention	outcome
Ruperto et al. [12]	Trial 1 was a 29-day, single-dose, randomized, double-blind, placebo-controlled study. 84 patients	Canakinumab	4mg/ kg subcutaneously or placebo administered	36 patients in total in the canakinumab group (84%), as opposed to 4 in the placebo group (10%), had an adapted JIA ACR 30 response at day 15 of trial 1, and this response was confirmed at day 29.
De Benedetti et al. [13]	Randomized control trial, double-blind placebo-controlled 112 children	tocilizumab	dose of 8 mg per kilogram of body weight (if the weight was ≥30 kg or 12 mg per kilogram if the weight was <30 kg) or placebo given intravenously every 2 weeks during the 12-week	At week 12, significantly more patients who received Tocilizumab than those who received a placebo met the primary outcome of a JIA ACR 30 response and an absence of fever
Huang zee and et al. [14]	Case report	tofacitinib	oral tofacitinib (2.5 mg twice daily) while maintaining oral methylprednisolone at 4 mg daily	The juvenile arthritis disease activity score (JADAS-10) decreased during the following two months, indicating that arthritis gradually improved. In line with this decrease in acute-phase reactants, serum ferritin levels were within the normal range (100.3 ng/mL). Clinical evaluation and the disease activity score showed that complete remission was attained after three months of treatment.

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Katherine Anne B Marzan 2012 [15]	Literature review; One RCT, one Prospective uncontrolled study, and one prospective observational study were reviewed.	adalimumab	.All patients received 24 mg/m ² of adalimumab (up to 40 mg) subcutaneously every other week throughout the 16- week open-label lead-in period, and they were divided into groups based on how often they used methotrexate.	An ACR Pedi 30 was achieved by 74.4% on adalimumab monotherapy and 94.1% on combination adalimumab and methotrexate treatment.
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Discussion

We reviewed a few articles that mentioned the presence of renal complications associated with juvenile idiopathic arthritis. We also studied articles that evaluated the use of monoclonal antibodies in JIA. We focused in this review on incorporating specific monoclonal antibodies in treating these renal manifestations.

Renal manifestations in juvenile idiopathic arthritis.

There have been incidences of renal involvement as a systemic effect of juvenile idiopathic arthritis.

In a case report by Chantarogh et al., 2017, the Occurrence of nephrotic syndrome and renal amyloidosis has been reported. In this report, a 19-year-old female patient with difficulty controlling symptoms of JIA has been reported. Renal amyloidosis was diagnosed through a renal pathologic examination that revealed eosinophilic amorphous material deposition in the interlobular arteries, arterioles, and interstitium. In addition, electron microscopy revealed fibrillary material deposits with diameters ranging from 8 to 10 nm [9].

A blood albumin level of 2mg/dL and a urine protein-to-creatinine ratio of 4/1 indicated nephrotic syndrome [9]. A renal biopsy demonstrated Congo red-positive fibril accumulation inside the glomeruli. Polarized light microscopy revealed the distinctive apple-green birefringence, indicating renal amyloidosis [9].

Another case report by Maleknejad et al. suggested findings of renal amyloidosis in a patient suffering from-

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Keywords

Juvenile idiopathic arthritis
Renal manifestations
Nephropathy
Monoclonal antibodies
Biological therapy
Tocilizumab